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Gastrointestinal dysmotility and pancreatic exocrine insufficiency in Donohue syndrome

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Gastrointestinal dysmotility and pancreatic insufficiency in two siblings with Donohue Syndrome

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Abstract:

Donohue syndrome is a rare congenital syndrome of insulin-resistance and abnormal glucose homeostasis, caused by mutations in the insulin receptor (INSR) gene. It is characterized by specific phenotypic and clinical features and the diagnosis is based on clinical, biochemical and genetic criteria.

We report two siblings with Donohue syndrome (cases 1, 2) with multiple clinical and biochemical characteristics. Both patients shared the same mutation and presented with intra-uterine growth restriction, failure to thrive, fasting hyperinsulinaemic hypoglycaemia and episodic post-prandial hyperglycaemia. Less common clinical features were also present, such as atrial septal defect and biventricular hypertrophy, clotting disorders, abnormal liver function tests and nephrocalcinosis. Interestingly, two previously unrecognized manifestations of the syndrome were also identified: severe gastrointestinal dysmotility (case 1) and exocrine pancreatic insufficiency (case 2).

The co-existence of all the above clinical features makes these cases extremely rare. Gastrointestinal dysmotility should always be considered as a potentially fatal feature in patients with the syndrome, due to the complexity of the possible co-morbidities. In addition, our clinical experience for the first time suggests that pancreatic exocrine insufficiency may offer a possible explanation for the growth retardation observed in some patients with this syndrome. Our finding that replacement treatment with pancreatic enzymes improved weight gain (case 2) implies that all patients with Donohue syndrome should be investigated for exocrine pancreatic insufficiency.

Key words: Donohue, gastrointestinal dysmotility, pancreatic exocrine insufficiency, insulin resistance, hyperinsulinism.

Introduction

Donohue syndrome is a rare autosomal recessive condition characterized by abnormal glucose homeostasis, severe insulin resistance and typical clinical and dysmorphic features. Common clinical findings include intrauterine and postnatal growth retardation, large and low-set ears, prominent eyes, broad nasal tip, enlargement of organs and soft tissues, reduced adipose tissue, muscular atrophy, a distended abdomen and enlarged external genitalia and nipples. Common biochemical findings include fasting hypoglycaemia, fasting hyperinsulinism, increased fasting C-peptide and post-prandial hyperglycaemia, with impaired insulin sensitivity being the underlying disorder (1).

The syndrome is caused by severe loss-of-function mutations in the insulin receptor (INSR) gene and was first described by Donohue in 1948 (2), and termed 'leprechaunism' in 1954 (3). The diagnosis is made on clinical, biochemical and genetic grounds. Donohue syndrome is the most severe type of INSR disorder and its prognosis is generally poor. Many affected patients die in infancy, with the majority not reaching the second year of life. Death is usually related to infections (4).

We report 2 siblings with Donohue syndrome who were observed to have additional clinical features (severe gastrointestinal dysmotility and pancreatic exocrine insufficiency) that have not been described previously.

Case reports

Here we report two cases of female infants with Donohue syndrome and highlight two additional clinical manifestations, which have not been reported previously (table 1).

Case 1: Female infant born at full term by elective Caesarian section for previous sections, with severe intrauterine growth retardation (IUGR) and a birth weight of 1.4 Kg (-5.28 SDS). She was survivor of a dichorionic diamniotic twin pregnancy and the other twin died in utero during the first trimester. She was the 5th child of consanguineous (first cousins) parents and her four siblings, aged 9, 7, 6 and 4 years, were all healthy, with no dysmorphic features or metabolic disorders. Multiple dysmorphic features were identified, including wrinkled skin all over the body with absence of cutaneous fat, microcephaly, hypertelorism, hypertrichosis, hypertrophied gums and lips. Additional clinical findings were mild clitoromegaly, mild breast enlargement, bilateral inguinal hernia and acanthosis nigricans.

Soon after birth she was noted to have pre-meal hypoglycaemia and post-feed hyperglycaemia. She had fasting insulin of >6945pmol/l and random insulin of 2634pmol/l and was started on Metformin. At the age of 3 months she was admitted to hospital with fever and was diagnosed with meningitis. At the age of 6 months, she was transferred to Great Ormond Street Hospital for multidisciplinary medical care. The blood glucose concentrations ranged between 3-14mmol/L and serum insulin levels were >300mU/L when plasma glucose was 9mmol/L. Treatment with recombinant IGF-1 was started for the management of hyperglycaemia at the initial dose of 35mcg/kg/day to a final dose of 90mcg/kg/day. Good glucose control was achieved with only few hypoglycaemic episodes, which responded to feeds.

Genetic analysis detected a homozygous INSR sequence variant, c.1093G>T, in exon 4 of the INSR gene. This mutation was predicted to result in an abnormal INSR protein, p.(Gly365Trp).{*Mutation Taster: Prediction disease causing (prob: 0.999999999999523). PolyPhen-2: PROBABLY DAMAGING with a score of 1.000*}. As far as we are aware, this variant has not been reported before, which is consistent with a diagnosis of Donohue syndrome. Sequence analysis of DNA from both parents, confirmed that they are both heterozygous carriers of this variant, indicating that it was biparentally inherited. The twin sibling possibly died of the same condition.

A cardiac echocardiogram revealed severe biventricular hypertrophy and secundum atrial septal defect (ASD) with moderate left to right shunt. The patient also had narrower right ear canal, as well as difficult airway, right-sided choanal atresia, small chest and required oxygen to maintain her saturation.

She subsequently developed abdominal distention and had a rectal biopsy. Hirschsprung disease was excluded, but the cause of the abdominal distention remained undefined. She was also noted to have elevated liver enzymes without hepatosplenomegaly. Clotting abnormalities of unknown cause were also present, with low levels of factors II, VII, IX and XI. Vitamin K supplementation was started at the age of 6 months.

Medullary nephrocalcinosis with mild hydronephrosis and enlarged ovaries with multicystic appearances were identified on renal and pelvic USS, respectively. Oestradiol and testosterone levels were raised. Significant failure to thrive and poor

growth development, a typical clinical characteristic of Donohue syndrome, was also manifest, as shown in the growth chart (figure 1).

At the age of 7 months, the patient's abdomen became acutely distended and her clinical picture was indicative of abdominal obstruction. She underwent distal ileostomy, but because of difficult intubation, 3 days after surgery she developed seizures secondary to global hypoxic brain injury with infarction of the cerebral hemispheres. The life-limiting diffuse brain damage in combination with deteriorating abdominal distension, desaturations and stoma losses that required fluid resuscitation, led to her death at the age of 10 months.

Case 2: This is the 7th child of the same parents, sibling of case 1, and is now 10 months old. She was delivered at 38⁺³ weeks of gestation by elective caesarean section and was small for gestational age, with a birth weight of 1.94 Kg (-3.52 SDS). Soon after birth, she developed hypoglycaemia with blood glucose concentration of 1.9mmol/L, which resolved with intravenous fluid administration of 10% dextrose and, subsequently, total parenteral nutrition (TPN). She was also noted to have mild facial dysmorphism, microcephaly and was also markedly hirsute. Her phenotypic features were characteristic of Donohue syndrome. Intermittent abdominal distension with distended bowel loops was noted from birth and was referred to our hospital on day 9 of life.

Donohue syndrome was confirmed by the same homozygous mutation in the INSR gene {c.1093G>T, p.(Gly365Trp)} as in case 1, found by fluorescent sequencing analysis.

In addition to hypoglycaemia on the first day of life, the patient exhibited fluctuating

blood glucose concentrations, ranging between 3-11mmol/L, with fasting hypoglycaemia and post-prandial hyperglycaemia, particularly after breastfeeding. Serum insulin levels were also very high (>300mU/L), which is in keeping with the diagnosis of Donohue syndrome.

Cardiac echocardiogram on day 9 of life showed a moderate sized secundum atrial septal defect, with mild but increasing signs of left to right shunt. The pulmonary arteries were enlarged and a modest concentric left ventricular hypertrophy was detected on day 20 of life, but could not be seen at the age of 5 months. An ASD repair and aortopexy were successfully performed.

Over the first 3 months of life there was progressive volume loss and partial collapse of the left lung. The enlarged left atrium or a plug compressed the left main bronchus presumably, and the trachea was slightly narrowed. Whereas dilated pulmonary artery branches probably caused compression of the airways, multiple consolidations on a CT scan were in keeping with aspirations. As a result, the patient suffered from respiratory distress with prolonged oxygen requirement. Muscular hypotonia of unknown origin, that could be an additional cause of the patient's respiratory distress, became apparent after the 5th month of life.

An additional clinical sign recurrent pyrexia associated with tachycardia and tachypnoea was present despite changes in antibiotic therapy and use of broad-spectrum antibiotics. Blood cultures were persistently negative and inflammatory markers were never raised. The cause of the pyrexia is unclear despite extensive investigations, including tuberculosis screen, but a potential focus could be the upper left lobe consolidation. Her umbilical cord was retained to beyond 1 month and, when separated, the umbilical stump looked clean and appropriately healed and there was

no evidence of omphalitis. She had otherwise normal skin and a normal neutrophil count. A basic immunodeficiency screen of lymphocyte subsets, T memory panel and basic immunoglobulins did not reveal any abnormalities.

Growth retardation and poor weight gain were also present on maximum feed volume and calories (figure 1).

Another clinical finding was mildly deranged clotting, disturbed liver function tests and low factor II, VII, IX and XI levels (table 2). Vitamin K1 and PIVKA-II (a functional marker of Vitamin K status) concentrations were undetectable.

On testing of her urine on the 21st day of life, there was increased excretion of calcium, with raised urine calcium/creatinine ratio. The ultrasound of both kidneys showed bilateral nephrocalcinosis. Urine albumin to creatinine ratio was also raised (table 2).

Moderate and severe pancreatic exocrine insufficiency was confirmed on two occasions (on day 49 and at 4 months of life, respectively) by abnormal pancreatic elastase-1 levels (table 2). Fat globules were also present in the faeces. Vitamin K and Vitamin D levels were undetectable and supplementation of both vitamins was required. Since the pancreatic exocrine insufficiency was treated with pancreatic enzymes, our patient's weight gain has improved (figure 1).

Discussion

Most of our patients' clinical features have been previously described in literature. ASD has been reported in extreme insulin resistance (Rabson-Medenthal phenotype) (5). Two cases of obstructive hypertrophic cardiomyopathy have been recently reported in patients with Donohue syndrome (6,7). A literature survey has revealed

that hypertrophic cardiomyopathy was present in 30% of patients with the syndrome and can be fatal (6).

Hyperbilirubinaemia and liver dysfunction (elevated AST and ALT, cholestasis and coagulation disorder) have also been reported in an infant with Donohue syndrome (8). With regards to renal function, a case of progressive obstructive cardiomyopathy and renal tubular dysfunction has been described (9). In addition, insulin receptor dysfunction has previously been associated with hypercalciuria and nephrocalcinosis, with no other consistent abnormality of renal function (10).

The co-existence of all the above clinical features, in association with the complexity and severity of the clinical presentations, makes these cases extremely rare. What is more, the identification of two clinical features that have not been previously reported in patients with insulin resistance syndromes, adds to the rarity of these cases. To the best of our knowledge, no data is available in the literature associating gastrointestinal dysmotility or pancreatic exocrine insufficiency with Donohue syndrome. The concurrence of two infrequent clinical entities in each of our patients either suggests that there is a wider, than previously estimated, variability in the clinical features of Donohue syndrome or, more likely, that our patients' parental consanguinity resulted in the expression of more than one disadvantageous recessive phenotypes. Our cases highlight the importance of recognising gastrointestinal dysmotility as a potentially fatal presentation of Donohue syndrome, due to the possible severe comorbidities of the patients with the syndrome. The exact underlying cause of the gastrointestinal dysmotility is still unclear. Early recognition and surgical input may improve the outcome.

In addition, the identification for the first time of pancreatic exocrine insufficiency in a patient with Donohue syndrome may provide an additional mechanism of growth retardation in these patients. It is well known that weight loss is one of the major clinical manifestations of pancreatic exocrine insufficiency, together with muscle wasting and steatorrhoea, as a result of malabsorption of essential nutrients, particularly fat. The most common conditions that cause pancreatic exocrine insufficiency are chronic pancreatitis, autoimmune pancreatitis, cystic fibrosis, Shwachman-Diamond syndrome, coeliac disease and Crohn's disease. Our finding that replacement with pancreatic enzymes enhanced our patient's growth and weight gain, further supports the hypothesis that pancreatic exocrine insufficiency contributed to the poor weight gain of this patient. Hence, we recommend that all patients with Donohue syndrome should be investigated for possible pancreatic exocrine insufficiency of all the possible causes, as it is a treatable clinical feature.

Conflict of interest:

None declared

Legends

Table 1: Clinical Phenotypic features of the 2 siblings (case 1 and case 2)

Table 2: Haematological and biochemical findings

Figure 1: Growth chart case 1 and case 2

Table 1: Clinical Phenotypic features of the 2 siblings (case 1 and case 2)

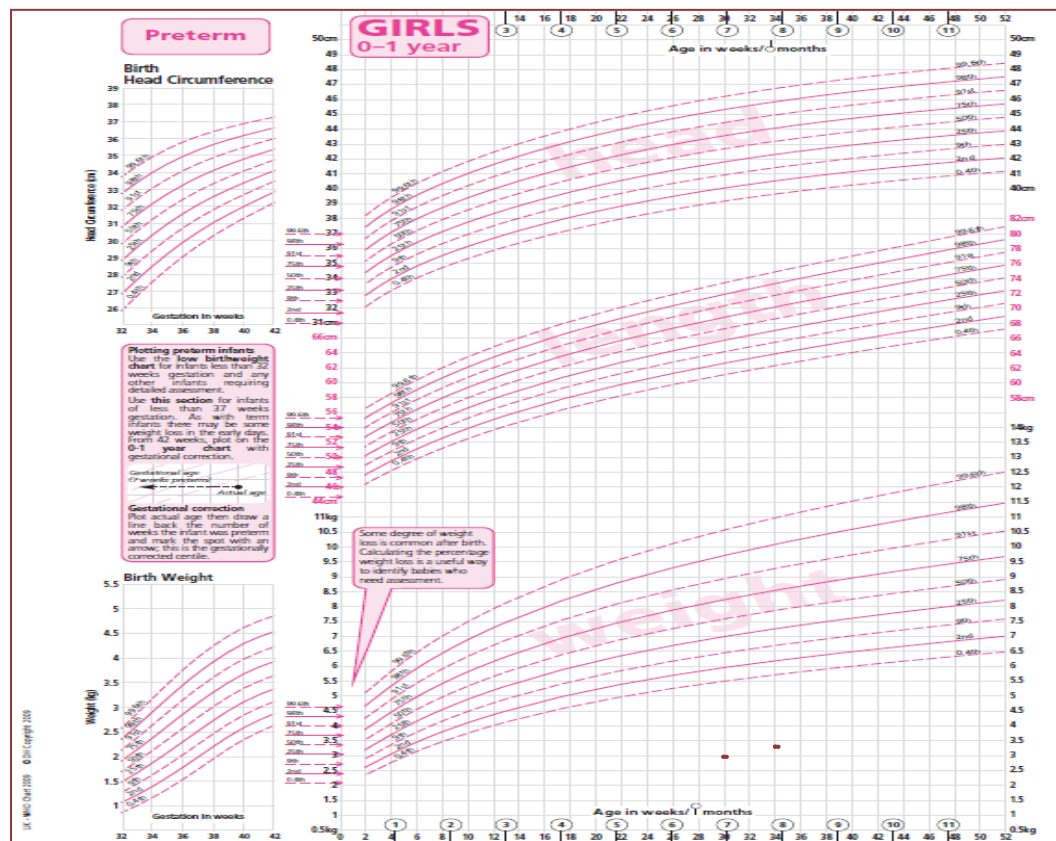
Clinical presentation/system review	Case 1	Case 2
IUGR	✓	✓
Failure to thrive postnatally	✓	✓
Dysmorphic features - Hypertrichosis	✓	✓
Abnormal glucose homeostasis	✓	✓
<u>Cardiovascular:</u>		
Biventricular hypertrophy - ASD	✓	✓
<u>Respiratory system:</u>		
Narrow ear canal, choanal atresia, small thorax	✓	×
Oxygen requirement	✓	✓
Dilated pulmonary artery branches	×	✓
<u>Gastrointestinal/Hepatobiliary system:</u>		
Abdominal distention	✓	✓
GI dysmotility	✓	×
Pancreatic exocrine insufficiency	×	✓
Liver dysfunction	✓	✓
<u>Others:</u>		
Clotting abnormalities (Factors II, VII, IX, XI)	✓	✓
Nephrocalcinosis-hydronephrosis	✓	✓
Muscular hypotonia	×	✓
Persistent pyrexia	×	✓
Enlarged ovaries	✓	×

Table 2: Haematological and biochemical findings

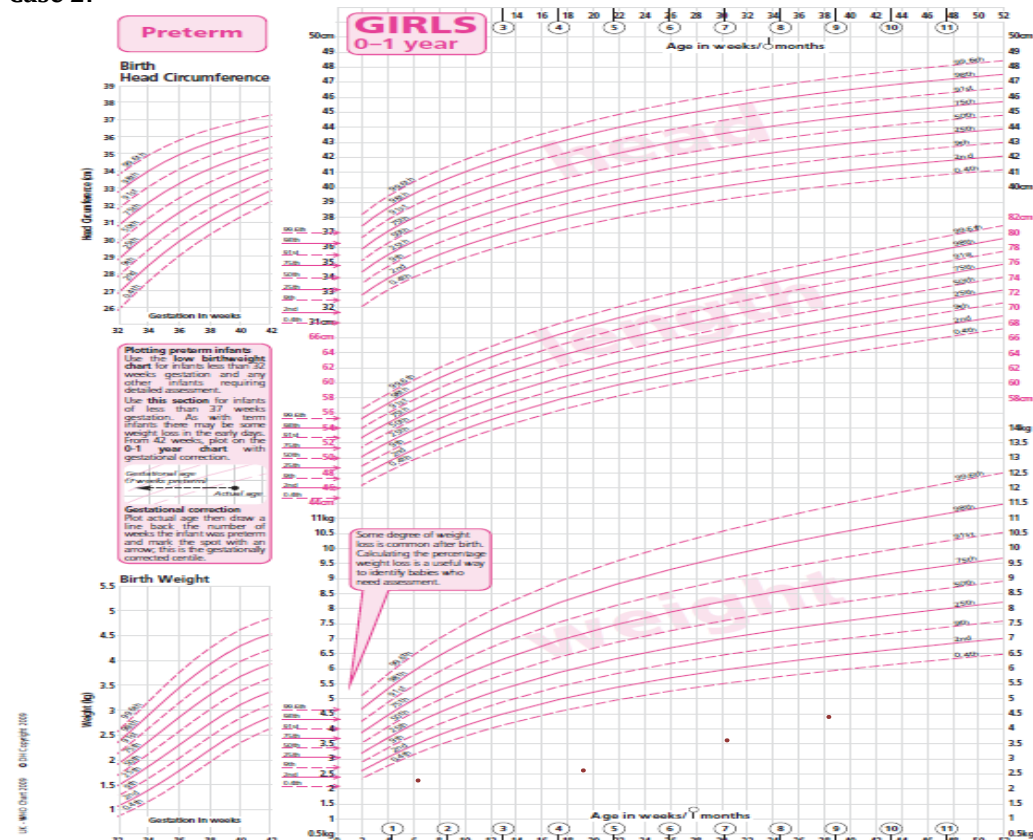
	Case 1		Case 2	
	At the time of admission (6 months of age)	Most recent (10 months age)	At the time of admission (9 days of life)	Most recent (10 months age)
Full blood count:				
Haemoglobin (g/L) (Normal range: 100-135)	99	78	99	98
White cell count (x10⁹/L) (Normal range: 6.0-18.0)	9.06	7.91	8.04	11.08
Neutrophils/Lymphocytes /Monocytes/Eosinophils (x10⁹/L)	3.58/3.9/1.19/0.37	3.42/2.88/0.81/0.78	1.92/4.98/0.83/0.3	4.95/4.66/1.26/0.16
Platelets (x10⁹/L) (Normal range: 150-450)	196	88	494	143
Clotting:				
Prothombin time (sec) (Normal range: 9.6-11.8)	20.1	22.6	16.1	15.3
APTT (sec) (Normal range: 28-40)	43.2	63.9	62.5	50.3
Fibrinogen (g/L) (Normal range: 1.7-4)	1.0	1.0	0.8	1.8
Factor assays:				
Factor II (IU/dl) (Normal range: 34-102)	30		32	
Factor V (IU/dl) (Normal range: 50-150)	101		129	
Factor VII (IU/dl) (Normal range: 42-138)	16		15	
Factor VIII (IU/dl) (Normal range: 50-125)	238.8		142.6	
Factor IX (IU/dl) (Normal range: 21-81)	16.1		19.3	
Factor XI (IU/dl) (Normal range: 27-79)	25		23	
Factor XII (IU/dl) (Normal range: 17-81)	65		52	
Liver Function test:				
Total bilirubin (µmol/L)	26	44	120	
Alanine transaminase (U/L) (Normal range: 12-47)	68	58	25	47
Albumin (g/L) (Normal range: 34-42)	32	20	20	31
GGT (U/L) (Normal range: 20-148)			473	
Renal Function test:				
Sodium (mmol/L)	136	137	142	145
Potassium (mmol/L)	4.4	3.5	5	3.8
Urea (mmol/L)	<0.7	5.4 (0.7-5.0)	0.9	12
Creatinine (µmol/L)	8	11 (13-32)	14	11
Urine Calcium/ creatinine ratio (mmol/mmol Creat) (Normal range: 0.06-0.74)	1.25	1.34 (0.09-2.2)	3.06	7.9
Urine albumin/creatinine ratio (mg/mmol) (Normal range: 1.7 - 12.2)			46.3	
Insulin (mU/L)	>300		>300	
Glucose (mmol/L)	8	8.25	4.5	9.16
Pancreatic elastase-1 (µg/g) (Moderate exocrine insufficiency: 100-199)	Not measured		197	>500 (post- replacement, at 5 months of age)

Figure 1: Growth chart case 1 and case 2

Case 1:



Case 2:



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